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Mini-Review

miRNAs as a Predictive Biomarker in Identifying Type 1 Diabetes: A Mini-Review

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ABSTRACT

In the contemporary world, Diabetes mellitus is the most documented metabolic disorder among school-going children and adolescents. This chronic condition, characterized by persistent hyperglycemia, poses significant health risks and necessitates early and accurate diagnosis to manage and mitigate its long-term complications effectively. Traditional diagnostic methods for Diabetes mellitus involve the measurement of various biomolecules, including glucose levels, glycated hemoglobin (HbA1c), and other related biomarkers. However, there is a growing interest in exploring more innovative and precise diagnostic tools, particularly in the realm of molecular biology. One such promising area of research involves micro ribonucleic acids (miRNAs), small non-coding RNA molecules that play crucial roles in gene regulation. Despite their potential, there is limited literature on the use of miRNAs in the diagnosis of Diabetes mellitus. miRNAs are known to influence the expression of genes involved in glucose metabolism, insulin secretion, and insulin resistance, making them valuable biomarkers for the disease. The current analysis aims to summarize the contemporaneous knowledge on the emerging role of miRNAs in Diabetes mellitus. Recent studies suggest that specific miRNAs are differentially expressed in diabetic patients compared to non-diabetic individuals, indicating their potential as diagnostic markers. For instance, miRNAs such as miR-375, miR-126, and miR-29 have been linked to pancreatic β-cell function, insulin signaling pathways, and inflammation, all of which are critical in the pathogenesis of Diabetes mellitus. The identification and validation of these miRNAs could revolutionize the diagnostic landscape, offering more sensitive and specific tools for early detection and monitoring of the disease in children and adolescents. This analysis seeks to shed light on the current understanding and future prospects of miRNA-based diagnostics in Diabetes mellitus, highlighting their potential to enhance clinical outcomes through early and precise intervention.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic ataxia affecting a varied aged population of about 350 million people in the current society[1]. Irrespective of its prevalence, it has evolved into an intercontinental issue connected with an increased mortality rate. The International Diabetes Federation (IDF) estimates, that over 552 people will be affected by diabetes by 2030[2]. DM is distinguished by an inadequate excretion of insulin from beta cells of the pancreas, which avoids the usual upkeep of glucose homeostasis in blood[3]. Insufficient insulin production narrows to type 1 diabetes mellitus, and an ineffective insulin response leads to type 2 diabetes. In the recent past, the prevalence of the spike in blood glucose globally reached about 6.4% and is projected to rise to 7.7% by 2030[4]. Between, type 1 and type 2 DM, type 1 is found to be the most regular chronic disease condition in the people of age group 13-18 years, representing about 10%, and in adolescents, up to 90% globally, which is to be increased by 3% annually[5]. Several mechanisms are involved in the origin of T1DM, comprising autoimmunity, susceptibility to genes, and epigenetic inference Autoantibodies averse to beta-cell antigens have been noticed since T1DM. In addition, mutations in different loci have been identified, followed by a varied number of tandem repeats that are situated in

the insulin gene. Other factors,like viral, epigenetic, and environmental, act directly on insulin genes that affect the onset of disease[6].

So far, several methods are in practice in the T1DM diagnosis with an estimation of autoantibodies as biomarkers. Even though many of them are found capable only after confirmation of clinical symptoms, it is necessary for new biomarkers that act as disease-identifiable aspects at an early stage[7]. In recent times, microRNAs, or miRNAs, have been identified as biological molecules that are connecting in the sickening of T1DM and its diagnosis through the regulation of gene expression[8]. This gene regulation happens in apoptosis, differentiation of cells, cell proliferation, and obstruction of protein synthesis by inhibiting translation or degrading mRNA[9].

Therefore, the present write-up is performed to unravel the biological pathways that are associated with miRNA biosynthesis, as well as their participation in the toxicity of T1DM.

History of miRNAs

miRNA was the term used formally by Ambros and Ruvkun's laboratories in the year 1993 when the lin-4 particle was recorded as miRNA, which was find first. miRNAs are defined as a group of tiny noncoding RNAs with 20 nucleotides that regulate gene voicing in the post-rewording stage, either by harmonizing gene expression or mRNA deterioration[10]. It is reported to have a gene situated in Caenorhabditis elegans that alters the developmental patterns of all stages of larvae. Reinhart et al identified miRNA, which is located, in Caenorhabditis elegans and commands the transition from L-4 to the spread of larvae. Given this, le-7 was noticed in humans which had a widespread therapeutic potential[11].

By then, several studies were conducted to investigate the character of these molecules in genes of mankind and their expression and involvement in the pathogenesis of disease[12,13].

Genesis, activity, and function of miRNA

The small noncoding RNA molecules called miRNAs have their genesis in intergenic miRNA genes or are encoded in introns in the form of hairpins[14]. RNA polymerases II /III transcripts genes of miRNA in the legal pathway which leads to principal miRNA with 5' cap and 3' cap polyadenylated tails. A protein complex with Drosha, DGCRB, and RNase III enzymes processes and cleaves precursor miRNA[15]. This process releases 70 nucleotides which are transferred with the help of Exportin 5 into Cytoplasm. Then miRNA duplex of approximately 22 base pair length is formed by the RNase enzyme Dicer and TAR RNA binding protein complex. Mature miRNAs then appear from both the strands that can be 3' or 5'. These mature micro RNAs along with Argonaute proteins (Ago) form RNA inducing silencing complex (RISC)[16]. RISC is essential to regulate gene expression by targeting specific mRNAs via complementary base pairing in the 3' region. This can end in mRNA destruction. During this gene silencing method, GW 182 proteins can communicate with Ago proteins. In other way, miRNAs arise from interweave and mitron evolution in non-canonical pathways and generate miRISC complex.

Micro RNAs regulate varied genes concerced in the division of cells and differentiation that could put up in understanding the origin and prognosis of deregulation that regulates malignancies like hematological cancers[17].

Role of miRNA in the secretion of insulin

Islet augment miRNAs work on a different order of downstream targets that influence insulin excretion. In one

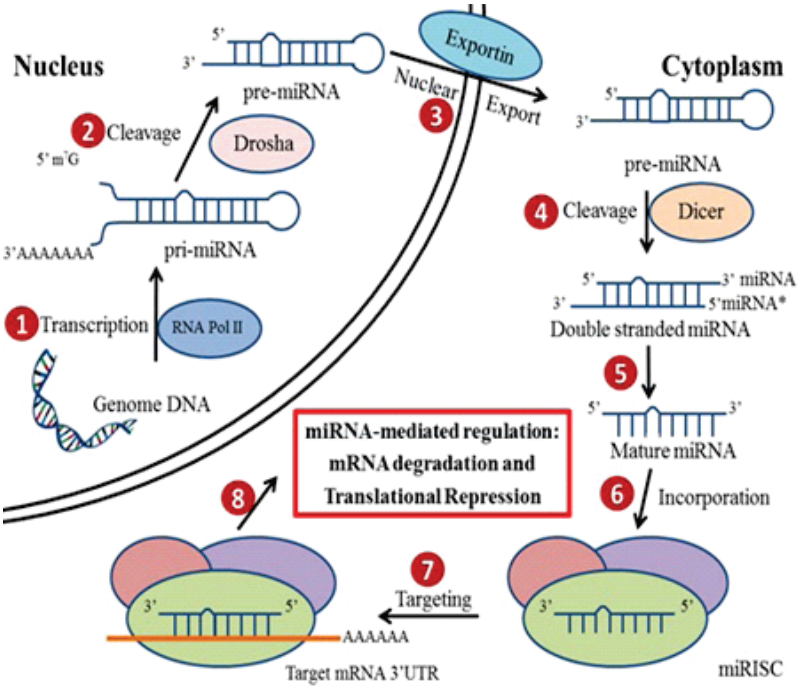

Figure 1: Biogenesis and Function of miRNA in Gene Expression [52]

study, a portrait of islet-derived miRNAs that sway insulin secretion by selecting beta cell exocytosis machinery is noted[18]. Significantly all the miRNAs screened in their study inhibited insulin secretion, suggesting an important part of islet miRNAs in preventing lethal hypoglycemia.By q RT-PCR methods, it is shown that miR-375 is expressed more in pancreatic islets and has a defined move in the down-functioning of insulin discharge. MiR-375 is also displayed to have high expression levels in murine insulinoma MIN 16 cells[19]. Consistent with that, an in vitro study stated that miR-375 overexpressed in mouse insulinoma Nit-1 cells and differed in a minimisation in GSIS through miR-375/Mtpn pick out interaction[20].

MiR-124a and miR 96 are known to impact exocytosis machinery in MIN6 cells. Surprisingly, miR-124 is shown to increase the secretion of insulin at basal glucose targets with lowering GSIS. Inhibition of Noc2 appearance by MiR-96 cal also decreases GSIS. MiR-7 is known to downregulate GSIS by modulating stages of the insulin exocytosis pathway[21].

Role of miRNA in insulin production

The lead of miR-375 in homeostasis of glucose further proceeds insulin trafficking and targets 3'-phosphoinositide-dependent protein kinase-1 (PDK1), a supreme product of the phosphatidylinositol 3-kinase (PI3K) cascade. The low measure of PDK1 are connected with less insulin gene expression concerning stimulation of blood glucose. However, high blood sugar situation yield a drop in precursor miR375 expression and the connected increase in PDK1 and levels of insulin[22]. Whereas MiR-204 is known to hurt the production of insulin. Thioredoxin-interacting protein (TXNIP) a conroller of redox states in beta cells induces the appearance of miR 204. TNXNIP is upregulated in diabetes and enhances the expression levels of miR 204[23].

Role of miRNA in beta cell proliferation and survival

Various pancreatic miRNAs control beta cellular pathways towards increasing cell division and survival and also beta cell damage convinced by the proinflammatory cytokines. As mentioned in the p13k footpath, miR-375 downregulates PKD expression and has an protective role in beta cell proliferation. In support of this, INS-1E cells tagged with a form of miR-375 which revealed a 25% reduction in expansion and viability[25].

MiR-21 is also participated in cellular machinery by managing beta cell number as it is called to play a pro-proliferative role in beta cell survival. MiR 200 is strongly correlated with the pathology of beta-cells in both types of diabetes[26].

Mechanism of action of miRNA

The main role of miRNA was to inhibit the process of translation by blocking the translation of coding genes or degrading mRNA[27-29]. These processes take place in the miRISC complex, which has an argonaute protein able to slice nuclei and make possible communication between miRNAs and their targets[30]. Perfect interaction complementarity results in messenger RNA partition and deterioration, and imperfect complementarity results in repression of translation. Few other reports revealed that miRNAs tend to devoted to specific UTR sequence ends i.e.; 3' untranslated region ends by causing deadenylation, decapping, and repression of translation[31]. The possible mechanisms of miRNAs are they can communicate with mRNAs of the nucleus by depleting translation[32]. Few other reports suggest its involvement in methylation sequences and genome remodeling. Additional mechanical action is its pairing capability with mRNA targets interfering with regulatory proteins. As reported, miRNAs are found to pick out gene promoters and initiate mRNA translation in defined conditions like cell cycle arrest and starvation of amino acids[33].

miRNAs: As Biomarkers and their implications in various diseases

miRNAs are connected with diseases like autoimmune and cardiovascular diseases, cancer, and neurodegenerative diseases and serve as biomarkers in early detection, prognosis, and treatment. miRNAs can predict the disease course and its response to treatment. Another important possibility is its easy isolation in varied biological species like blood, serum, plasma, tissues, and urine. An additional advantage is its durability and protection from the presence of exosomes and microsomes, which help in shell protection. Amplification of nucleic acids and sequencing serve as miRNA identification techniques in various biospecimens. The miRNA voicing can be detected by blotting techniques, hybridization, quantitative real-time PCR (qPCR), and next-generation sequencing (NGS).[34-36].

Concerning its implications for cancer, several studies have reported the regulatory impact of miRNA. In this regard, miRNA-15 and 16 were the downregulated molecules seen in lymphocytic leukemia patients. Few other reports have demonstrated that deregulation of miRNA increases the risk of breast cancer. Several other studies demonstrated the character of miRNA in the pathways of tumors. miRNA-15 and 16 were identified to have a key role in anti-apoptotic repression by B-cell lymphoma expression. All these put together will be able in detecting disease markers[37,38].

Various other studies from the literature proved that miRNA is involved in deregulation in Burkitt lymphoma infected by Epstein Barr Virus (EBV), polyomavirus followed by herpes virus, and HIV. The reported literature shows that miRNAs are involved in the regulation of cardiac occurrence and preservation. The pathways of CVD, where miRNAs participate are arrhythmias, atherosclerosis, myocardial ischemia, and cardiac hypertrophy[39]. Several studies have reported MiR-1, 126, 197, 208 and MiR 223 have a diagnostic impact as biomarkers in acute myocardial infarction. MiRNA-34, 155, and 326 are upregulated in

systemic lupus erythematosus (SLE) as low indications of miRNA 146 are conducted with a high risk of SLE. Few more reports suggested the role of miRNA as a biological marker in human chorionic gonadotropin (hCG) and the abundance of miR-16, 23, 29, 107, and 523 were found to be linked with Crohn's disease. MiR-1, 133, and 223 are measured in autosomal dominant polycystic kidney disease[40-42].

miRNA as a key player in T1DM

As previously reported about the expression of miRNA in biological pathways, One such is glucose consumption. Steadiness in the discharge of glucose relies on pancreatic beta-cell equilibrium. Pancreatic beta cells induce the secretion of insulin when there are elevated blood glucose levels, which results in glucose uptake by peripheral tissues that reduce blood levels. Studies reported that a huge amount of miRNA is included in the homeostasis of the pancreas and various other studies endeavored to find certain miRNA particles that dysregulate pancreatic beta cell perfect function, enhancing apoptosis[43-45].

One such example is miRNA-21 which overexpresses and disrupts the development of beta cells in T1DM, as reported in the literature[46]. Moreover, literature reports elevated miR-21 in diabetes by targeting the BCL-2 gene. Reports suggest another miR-29 that is seen in mice that impairs glucose-induced insulin secretion. Upregulation of MiR-181 was also seen in T1DM patients by negative correlation with C-peptide. Reports also demonstrate the impact of MiR-7 and miR-124 in the pancreatic differentiation pathway of endocrines in diabetic individuals[47].

While T1DM is an autoimmune disease, the role of B lymphocytes is significant. The study has demonstrated that MiR-34a overexpression is associated with B lymphocyte capacity reduction in diabetic mice. On the other side, overexpression of miR-23, miR-98, and miR-50 is found to initiate the CD8+ T cells productivity which targets islet antigens by mimicking tumor necrosis factor-related apoptosis-inducing FAS ligand gene appearance[48,49]. This has been shown to indicate a gene silencing mechanism and initiates the autoimmune system and subsequently T1DM onset.

There are three major antibodies, that are present in T1DM patients (antigen IA-2, IA-2b, and glutamic acid decarboxylase (GAD). miRNAs might be connected in the biosynthesis of antibodies, as reported[50]. However, MiR-9 and 30 are also connected with insulin gene amplification, and MiR-25 targets the INS gene, which causes repression of translation inhibiting the emission of insulin that leads to the pathogenesis of T1DM[51].

CONCLUSION

Diabetes mellitus, a metabolic disease is rising in every part of the world leading to adverse health complications. The asymptomatic condition of diabetes mellitus throws a light to intervene in disease progression. Studies on early diagno-sis of disease play a vital role in preventing complications. Screening on new biomarkers for thediseases aims at a thorough understanding of the disease and can help detect disease in the early stage. Among various screened markers, miRNAs are reported to detect the condition of presenting disease, especially T1DM. These can be extracted from varied cell types and biotic fluids that denote adaptation in the succession of disease, like dysfunction of beta cells and death. mi RNAs can be deliberated in varied cell kinds like plasma, serum, tissue, and urine. Their role has transformed it into a major factor in the pathological process of disease. As miRNAs are implicative of pathways in the autoimmune system and insulin gene expression that lead to the pathogenesis of the disease. In recent times, several studies proved that miRNAs might be a promising biomarker in diabetes mellitus identification.

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